REMARKS

Claims 45-60 presently appear in this case. The previously appearing claims had been subject to a restriction requirement. No claims have been allowed. The official action of January 30, 2003, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method which is now known in the art as autoimmune neuroprotection. It has been discovered that neuronal degeneration caused by the neurodegenerative effects of disease or secondary neuronal degeneration that follows the primary neuronal damage of an injury can be reduced if steps are taken to cause T cells activated against an NS-specific antigen which, in its native state, is present at the site of neuronal degeneration, to accumulate at the site of neuronal degeneration. The mere presence of these activated T cells at the site of injury causes a cytokine response that has a significant effect in reducing the neuronal degeneration. The preferred methods of causing the T cells to accumulate at the site of injury is to either administer T cells activated against an NS-specific antigen, which in its native state is present at the site of the injury, or to administer the antigen itself in such a way as to cause a T cell response such that T cells become

activated against the NS-specific antigen which is present at the site of neuronal degeneration.

The interview among examiners, Bunner and Kunz, the inventor, Prof. Michal Schwartz, and the undersigned attorney, which interview was also attended by examiners Turner, Kemmerer, and Nichols, on June 26, 2003, is hereby gratefully acknowledged. In this interview, Prof. Schwartz presented a slide presentation explaining the work of her laboratory that resulted in the present invention and the subsequent work which has been done in proving broad applicability of the present invention. This work has been published in prestigious journals, copies of which are being made of record herewith. Claim wording that might appropriately claim the full breadth of this invention without reading on the prior art and in full compliance with 35 USC 112 was discussed at the interview. While no agreements were reached, it is believed that the examiners now have a better understanding of the present invention, and that in additional discussions, the examiners can help applicants in appropriate wording of the claims in order to obtain appropriate protection for this important and novel advance in the art.

All of the claims in this application have now been deleted in favor of new claims 45-60. The new claims submitted herewith attempt to adopt the language that was

discussed at the interview. If this language is not considered to put this case into condition for allowance, it is respectfully requested that the examiner contact the undersigned to schedule a further interview to discuss language for this case that might be acceptable.

Support for the language of new claims 45 and 53 may be found in the specification. For example, paragraph 119, at page 49, discloses that the invention may be used to ameliorate the effects of disease that result in a degenerative process. Paragraph 118, on page 49, discloses the inhibition of secondary degeneration that may otherwise follow primary NS injury. With respect to claim 53, note paragraph 2, on page 1, which states that the present invention relates to methods to "ameliorate the effects of injury or disease of the nervous system". Support for the definition of NS-specific antigen appears at paragraph 24, on page 9, where it states:

> The term "NS-specific antigen" as used herein refers to an antigen of the NS that specifically activates T cells such that following activation the activated T cells accumulate at a site of injury or disease in the NS of the patient.

See also paragraph 95, at page 39. Paragraph 96, at pages 39 and 40, discloses that the NS-specific antigen is one which in its native state is in tissue at the site of CNS injury or disease. The immunogenic and cryptic peptides are disclosed

at paragraphs 105 to 107, at pages 43-44. Accordingly, it is submitted that the newly presented claims are fully supported by the written description of the present specification.

It should be noted that the present claims specify that when the individual in need has an autoimmune disease, the NS-specific antigen is not the autoimmune antigen of that disease, and when the individual in need has a neoplasm, the NS-specific antigen is one that does not appear in the antigen. This language is supported in paragraph 121 at pages 50-51 of the present specification. The first proviso is inserted so as to exclude embodiments that exacerbate an autoimmune disease. The second proviso is added so that the claim will not read on prior art antineoplastic immunotherapy.

The examiner has deemed the previous restriction requirement to be proper and has made it final. It is urged, however, that new claims 45 and 53 are linking claims that appropriately claim the full breadth of the present invention. The main step of both claims is causing T cells activated against an NS-specific antigen, which in its native state is present at the site of neuronal degeneration, to accumulate at the site of neuronal degeneration in the individual in need, thereby reducing neuronal degeneration at that site or ameliorating the effects of the injury or disease at that site. This is generic to preferred methods of active and

passive administration of such T cells as claimed in claims 46 and 47 and claims 54 and 55. Furthermore, as was explained in the interview, the effect of the invention is the same whether treating secondary degeneration caused by an injury or the degeneration caused by a disease. Accordingly, it is again respectfully requested that the restriction requirement be reconsidered and withdrawn in view of the presence of the linking claims submitted hereby.

It is noted that the examiner has crossed out two citations from the IDS, but only because the citations were already referenced. Accordingly, it is understood that all of the references submitted have been considered and will appear on the front page of any patent which may issue in this case.

The examiner states that the oath or declaration is defective because of non-initialed and/or non-dated alterations.

The only non-initialed or non-dated alteration appears to be in the residence and post office address of inventor Moalem. However, it is not necessary that this information appear in the declaration if it appears in an application data sheet. Attached hereto is an application data sheet submitting the correct information as to the residence and post office addresses of all the inventors, which supersedes the data in the originally filed declaration.

Accordingly, it is submitted that in view of this application data sheet, it is no longer necessary to have the declaration re-executed.

The examiner has objected to the specification for a number of reasons. The examiner states that the status of the applications at pages 5 and 58 should be updated and, presumably, also at page 1. The examiner states that the brief description of the drawings at page 22 does not refer to figures 18A and 18B and that the title of the invention is not descriptive.

The serial numbers have now been reviewed and were updated as applicable. The serial numbers at pages 1 and 5 are still pending. The one at page 58 is now U.S. patent 6,267,955 and this number has been substituted for the reference to the serial number.

The brief description of the drawings has been amended as suggested by the examiner. The title has been amended to read:

> A METHOD FOR REDUCING NEURONAL DEGENERATION SO AS TO AMELIORATE THE EFFECTS OF INJURY OR DISEASE

It is believed that this title is now descriptive of the presently claimed invention. Accordingly, reconsideration and withdrawal of the objection to the disclosure is respectfully urged.

The examiner has objected to claims 1, 2, 31 and 41 as reciting non-elected groups and species.

These claims have now all been deleted. It is believed that the restriction requirement is now moot in view of the presentation of new claims.

Claims 1, 31, 32 and 41 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 6, 7 and 16 of co-pending application number 09/218,277.

As neither the present application nor the '277 application have allowable claims, it is respectfully requested that this provisional rejection be held in abeyance until allowable subject matter is indicated in one or the other of the applications. At that time a decision can be made whether to maintain a line of distinction between the claims, to abandon one of these applications, or to file a terminal disclaimer. Accordingly, it is requested that this rejection be held in abeyance, in accordance with 37 CFR §1.111(b), until allowable subject matter is indicated in accordance with 37 CFR §1.111(b).

Claims 1, 2, 31, 32, 38, 39 and 41 have been rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a method for promoting recovery from spinal cord injury comprising subcutaneously

administering to an individual in need thereof a composition comprising a peptide derivative from Nogo-A and wherein said composition promotes recovery from spinal cord injury, does not reasonably provide enablement for a method for preventing or inhibiting neuronal degeneration in the central nervous system for ameliorating the effects of injury commensurate in scope with the claims. This rejection is respectfully traversed.

Prof. Schwartz made a comprehensive presentation explaining why predictions made in the present specification have been proved to be accurate. So many embodiments have been successfully tested that it would no longer be unexpected that the full scope of the present invention would work as disclosed. Furthermore, it would not take undue experimentation to make and use the invention with respect to other NS-specific peptides or other neurodegenerative diseases or injuries.

Attached hereto are the following thirty-eight references from the laboratory of the present inventors relating to the present invention as well as to related improvements that are based on the same concept:

YOLES et al., "Degeneration of Spared Axons Following Partial White Matter Lesion: Implications for Optic Nerve Neuropathies", *Experimental Neurology*, 153:1-7 (1998)

MOALEM et al., "Autoimmune T Cells Protect Neurons from Secondary Degeneration after Central Nervous System Axotomy", *Nature Medicine*, 5:49-55 (1999)

SCHWARTZ et al., "Innate and Adaptive Immune Responses Can Be Beneficial for CNS Repair", *TINS*, 22:295-299 (1999)

SCHWARTZ, "Vaccination for T Cell-Mediated Neuroprotection: Dream or Reality?", *Drug Development Research*, 50:223-225 (2000)

HAUBEN et al., "Autoimmune T Cells as Potential Neuroprotective Therapy for Spinal Cord Injury", *The Lancet*, 354:286-287 (2000)

SCHWARTZ et al., "Neuroprotection: A New Treatment Modality for Glaucoma?", *Current Opinion in Ophthalmology*, 11:107-111 (2000)

KIPNIS et al., "T Cell Immunity to Copolymer 1 Confers Neuroprotection on the Damaged Optic Nerve: Possible Therapy for Optic Neuropathies", *PNAS*, 97:7446-7451 (2000)

MOALEM et al., "Autoimmune T Cells Retard the Loss of Function in Injured Rat Optic Nerves", *Journal of Neuroimmunology*, 106:189-197 (2000)

HAUBEN et al., "Passive or Active Immunization with Myelin Basic Protein Promotes Recovery from Spinal Cord Contusion", *The Journal of Neuroscience*, 20:6421-6430 (2000)

MOALEM et al., "Production of Neurotrophins by Activated T Cells: Implications for Neuroprotective Autoimmunity", *Journal of Autoimmunity*, 15:331-345 (2000)

SCHWATRZ, "T Cell Mediated Neuroprotection is a Physiological Response to Central nervous System Insults", *J Mol Med*, 78:594-597 (2001)

FISHER et al., "Vaccination for Neuroprotection in the Mouse Optic Nerve: Implications for Optic Neuropathies", *The Journal of Neuroscience*, 21:136-142 (2001)

SCHWARTZ et al., "Beneficial Immune Activity after CNS Injury: Prospects for Vaccination", *Journal of Neuroimmunology*, 113:185-192 (2001)

BUTOVSKY et al., "Morphological Aspects of Spinal Cord Autoimmune Neuroprotection: Colocalization of T Cells with B7-2 *(CD86)* and prevention of Cyst Formation", *The FASEB Journal*, express article 10.1096/fj.00-0550fje, published online February 26, 2001

SCHORI et al., "Vaccination for Protection of Retinal Ganglion Cells Against Death from Glutamate Cytotoxicity and Ocular Hypertension: Implications for Glaucoma", *PNAS*, 98:3398-3403 (2001)

YOLES et al., "Self-Protection Mechanism Awakened by Glutamate in Retinal Ganglion Cells", *Journal of Neurotrauma*, 18:339-349 (2001)

YOLES et al., "Protective Autoimmunity Is a Physiological Response to CNS Trauma", *The Journal of Neuroscience*, 21:3740-3748 (2001)

SCHWARTZ et al., "Protective Autoimmunity: Regulation and Prospects for Vaccination after Brain and Spinal Cord Injuries", *TENDS in Molecular Medicine*, 7:252-258 (2001)

KIPNIS et al., "Neuronal Survival after CNS Insult Is Determined by a Genetically Encoded Autoimmune Response", *The Journal of Neurosciences*, 21:4564-4571 (2001)

HAUBEN et al., "Posttraumatic Therapeutic Vaccination with Modified Myelin Self-Antigen Prevents Complete Paralysis While Avoiding Autoimmune Disease", *The Journal of Clinical Investigation*, 108:591-599 (2001)

FISHER et al., "Increased Post-traumatic Survival of neurons in IL-6-Knockout Mice on a background of EAE Susceptibility", *Journal of Neuroimmunology*, 119:1-9 (2001)

SCHORI et al., "T-Cell-Based Immunity Counteracts the Potential Toxicity of Glutamate in the Central Nervous System", *Journal of Neuroimmunology*, 119:199-204 (2001)

HAUBEN et al., "Vaccination with a Nogo-A-Derived Peptide after Incomplete Spinal-Cord Injury Promotes Recovery Via a T-Cell-Mediated Neuroprotective Response: Comparison with Other Myelin Antigens", *PNAS*, 98:15173-15178 (2001)

SCHWARTZ et al., "Differing Views on Spinal Cord Repair", *Science*, 296:1400 (2002)

KIPNIS et al., "Dual Action of Glatiramer Acetate (Cop-1) in the Treatment of CNS Autoimmune and Neurodegenerative Disorders", *TRENDS in Molecular Medicine*, 8:319-323 (2002)

SCHORI et al., "Immune-Related Mechanisms Participating in Resistance and Susceptibility to Glutamate Toxicity", *European Journal of Neuroscience*, 16:557-564 (2002)

BAROUCH et al., "Autoreactive T Cells Induce Neurotrophin Production by Immune and Neural Cells in Injured Rat Optic Nerve: Implications for Protective Autoimmunity", *The FASEB Journal*, 16:1304-1306 (2002)

KIPNIS et al., "Myelin Specific Th1 Cells Are Necessary for Post-Traumatic Protective Autoimmunity", *Journal of Neuroimmunology*, 130:78-85 (2002)

SCHORI et al., "Severe immunodeficiency Has Opposite Effects on Neuronal Survival in Glutamate-Susceptible and -Resistant Mice: Adverse Effect of B Cells", *The Journal of Immunology*, 169:2861-2865 (2002)

SCHWARTZ et al., "Multiple Sclerosis as a By-Product of the Failure to Substain Protective Autoimmunity: A Paradigm Shift", *The Neuroscientist*, 8:405-413 (2002)

HAUBEN et al., "Sexual Dimorphism in the Spontaneous Recovery from Spinal Cord Injury: A Gender Gap in beneficial Autoimmunity?", *European Journal of Neuroscience*, 16:1731-1740 (2002)

MIZRAHI et al., "The Tissue-Specific Self-Pathogen Is the Protective Self-Antigen: The Case of Uveitis", *J Immunol*, 169:5971-5977 (2002)

KIPNIS et al., "Neuroprotective Autoimmunity: Naturally Occurring $CD4^+CD25^+$ Regulatory T Cells Suppress the Ability to Withstand Injury to the Central Nervous System", *PNAS*, 99:15620-15625 2002)

SCHWARTZ et al., Autoimmunity on Alert: Naturally Occurring Regulatory $CD4^+CD25^+$ T Cells as Part of the Evolutionary Compromise Between a 'Need' and a 'Risk", *TRENDS in Immunology*, 23:530-534 (2002)

HAUBEN et al., "Therapeutic vaccination for Spinal Cord Injury: Helping the Body to Cure Itself", *TRENDS in Pharmacological Sciences*, 24: 7-12 (2003)

SCHWARTZ, "Macrophages and Microglia in Central Nervous System Injury: Are They Helpful or Harmful?", *Journal of Cerebral Blood Flow & Metabolism*, 23:358-394 (2003)

ANGELOV et al., "Therapeutic Vaccine for Acute and Chronic Motor Neuron Diseases: Implications for Amyotrophc Lateral Sclerosis", *PNAS*, 100:4790-4795 (2003)

SCHWARTZ et al., "Protective Autoimmunity Against the Enemy Within: Fighting Glutamate Toxicity", *Trends Neurosci*, 26:297-302 (2003)

The basic paper is Moalem et al, Nature (1999). Halben, J. Neurosci. (2000) expands the original work in the optic nerve to spinal cord contusion, including both active and passive administration. This proves the concept that the same active T cells work in radically different sites. Fisher et al, J. Neurosci. (2001), disclose active and passive vaccination to raise T cells specific to various NS-specific proteins. Butovsky et al, FASEB J (2001), show a proof of mechanism establishing that T cells get to the site of the lesion in the spinal cord. Schori et al, PNAS (2001), is an important paper relating to glutamate and glaucoma, establishing that COP 1 works where there is no myelin and MBP does not work. Yoles et al, J. Neurosci. (2001), shows the beneficial aspect of passive transfer of T cells. Hauben et al, J.C.I. (2001), disclose experiments that altered peptides work in order to obtain the benefit of neuroprotection. It should be understood that this paper won an award as one of

the ten leading papers of the year for this journal. Hauben et al, PNAS (2001), shows active and passive vaccination with Nogo A. Misrachi et al, J. Immunol. (2002), is important in showing that the specificity of the antigen for beneficial autoimmunity is determined by the site and not by the type of insult. Angelov et al, PNAS (2003), shows the operability of the present invention in the PNS.

It is urged that these papers establish for the record what Prof. Schwartz was able to explain at the interview. In light of all the experiments that have been done with respect to this invention since the effective filing date of the present application, the full scope of the present invention would be expected to be operable. There is no reason to believe that undue experimentation would be involved in order to make and use the full scope of the present invention. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 1, 2, 31, 32, 38, 39 and 41 have been rejected under 35 USC 112, second paragraph, as being indefinite. This rejection is respectfully traversed. All of the claims previously in the case have now been deleted. It is not believed that any of the grounds of indefiniteness noted by the examiner are applicable to the new claims.

Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

The art made of record by the examiner has been noted, as has the examiner's implicit recognition that none are sufficiently pertinent to warrant their application against the claims. It is further noted that none of the cited publications have an effective date prior to the effective filing date of the present application.

It is submitted that all of the claims now present in the case clearly define over the references of record, and fully comply with 35 USC 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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